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New Japanese Initiatives on Stem Cell Therapies

Kenji Konomi,[1,*] Morikuni Tobita,[1] Kenichi Kimura,[1] and Daisaku Sato[2]
[1]Research and Development Division, Health Policy Bureau, Ministry of Health, Labour and Welfare, 1-2-2, Kasumigaseki, Chiyoda-ku, Tokyo 100-8916, Japan
[2]Pharmaceuticals and Medical Devices Agency, 3-2-2 Kasumigaseki, Chiyoda-ku, Tokyo 100-0013, Japan
*Correspondence: jzt02060@nifty.ne.jp
http://dx.doi.org/10.1016/j.stem.2015.03.012

Two laws aiming to provide a new legal framework to promote regenerative medicine, while ensuring the efficacy and safety of the treatments, came into effect in Japan on November 25, 2014. The scope of these laws is briefly described here.

Introduction

Prior to 2014, there were no statute-based regulations in Japan providing oversight for regenerative medicine, including stem cell therapies, other than pharmaceutical regulations that covered cellular and tissue-based products. During this time, Japan was unable to safeguard against patients, including foreigners, seeking unproven stem cell therapy (so-called medical tourism), and as a result, some patients seeking treatment experienced severe and even life-threatening problems (Editorial, 2013). On the other hand, regenerative medicine, including the use of induced pluripotent stem cells (iPSCs), is an important component of healthcare strategy in Japan, whose population has the one of the highest proportions of aged individuals in the world and is expected to increase. For these reasons, a new regulatory framework was required for regenerative medicine, and to meet this need, two laws known as the "The Act on the Safety of Regenerative Medicine" (http://www.hourei.mhlw.go.jp/cgi-bin/t_docframe2.cgi?MODE=hourei&DMODE=SEARCH&SMODE=NORMAL&KEYWORD=%8d%c4%90%b6%88%e3%97%c3%93%99&EFSNO=229&FILE=FIRST&POS=0&HITSU=306) and the "Pharmaceuticals, Medical Devices and Other Therapeutic Products Act" (http://www.hourei.mhlw.go.jp/cgi-bin/t_docframe.cgi?MODE=hourei&DMODE=CONTENTS&SMODE=NORMAL&KEYWORD=&EFSNO=638) came into effect on November 25, 2014. Here, we provide a description of the new regulations and approval process, and we discuss how the new regulations address deficiencies in the previous system.

The Act on the Safety of Regenerative Medicine

The Act on the Safety of Regenerative Medicine regulates medical professionals' practices and clinical studies related to regenerative medicine, which had previously been under the jurisdiction of the Medical Practitioners' Act and the Medical Care Act. The new Act sets out regulations not only for "regenerative medicine" to reconstruct or repair human structures and functions, but also for cell-based therapies such as cancer immunotherapy. Prior to the new regulations, clinical studies involving human stem cell therapies were conducted according to guidelines known as "the human stem cell clinical research guidelines," which were not legally binding. However, the new Act sets out legal regulations not only for research, but also for the daily practice of cell therapy without approved regenerative medical products.

Medical technologies that use items such as stromal vascular fraction (SVF), which have recently become an issue in the United States, will be regulated in Japan under the Act (Dolgin, 2014).

This law divides regenerative medicine into three categories, depending on the potential risks (Table 1). For example, the level of risk associated with medical treatment that uses SVF would be considered as either medium or low. Any plan to use regenerative medicine has to be submitted to the Ministry of Health, Labour and Welfare (MHLW) regardless of which of the three risk categories the treatment falls into. Additionally, a medical institution that wishes to offer regenerative medicine must solicit opinions from a certified special committee or a certified committee for regenerative medicine about their regenerative medicine provision plan before they can submit the plan to the MHLW (Figure S1). These committees are considered as fulfilling the legally stipulated accreditation criteria by the MHLW. After obtaining the committee's opinion, whether it recommends approval or not, the medical institution can submit their regenerative medicine provision plan, accompanied by the opinion of the committee, to the MHLW. Furthermore, after the initial submission is filed, the medical institution is obligated to report adverse events and annual details about the level of implementation, such as the name of the provided regenerative medicine, number of patients treated, and evaluation of the treatment, to the MHLW and the committee. The MHLW will periodically publish a summary based on these reports to assure transparency of medical institutions that provide regenerative medicine. The availability of this data is important, because the full picture of regenerative medicine (including cell therapy) activities, which have been performed without restriction to date, has been unclear; the real status of these therapies is expected to become apparent as a result of the Act. Although there have been suggestions that self-reporting is not enough, the Act will enable the MHLW to get a comprehensive picture of the regenerative medicine that is actually being practiced for the first time, and it is therefore an important step in securing the medical safety of the Japanese population.

A high profile example of a study that would be affected by the new Act is the world's first transplantation of retinal pigmentation epithelial cells developed from human iPSCs, which was performed as a clinical study by Dr. Takahashi's group in September 2014 (Reardon and

Table 1. Classification of Regenerative Medical Technologies According to Risk

Category	Example of Cells Used for Regenerative Medicine	Example of Treatments
Class I (high risk)	iPSCs, ESCs, cells into which a gene is introduced, xenogeneic cells, allogeneic cells	transplantation of retinal pigment epithelium cells derived from autologous iPSCs, ex vivo gene therapy
Class II (medium risk)	autologous somatic stem cells	autologous mesenchymal stem cell infusion therapy for liver cirrhosis
Class III (low risk)	autologous somatic cells	cancer immunotherapy

Regenerative medical technologies are divided into three classes depending on the potential risk to human health.

Cyranoski, 2014). Regenerative medicine studies using human iPSCs such as this will be placed in the high-risk medical technology category. Under the Act, studies falling into the highest risk category of the three classes require review at the national level. After submission of a provision plan to provide regenerative medicine that is classified as high-risk to the MHLW, the MHLW can postpone implementation of the proposed plan for a maximum of 90 days. According to the Act, the MHLW must review the appropriateness of the plan by consulting the Health Science Council within the 90-day period. The duration of the review is shorter than similar procedures in the previous system to ensure consistency in the review process under human stem cell clinical research guidelines.

The Act on the Safety of Regenerative Medicine stipulates usage of GMP-type facilities/equipment and quality control requirements for cell processing facilities that manufacture cells for clinical study and medical treatment. These requirements are designed to ensure safety and are concerned with the facilities and equipment, as well as manufacturing and quality control. If processed cells are manufactured in a medical institution, notification to the MLHW is necessary, declaring that the cell processing facility complies with the aforementioned requirements. If processed cells are manufactured locally by an entity such as a company that is not part of a medical institution, the entity must obtain a manufacturing license from the MHLW, then receive an inspection by the Pharmaceuticals Medical Devices Agency (PMDA) to check adherence to the requirements. If processed cells are manufactured outside the country, the manufacturer is subject to the same requirements as local Japanese manufacturers.

In short, the Act seeks to promote regenerative medicine by facilitating clinical studies, even those involving companies, while ensuring safety. After this phase of clinical studies, clinical trials are regulated by the Pharmaceuticals, Medical Devices and Other Therapeutic Products Act.

Pharmaceuticals, Medical Devices and Other Therapeutic Products Act

The Pharmaceutical Affairs Law was revised and renamed the Pharmaceuticals, Medical Devices and Other Therapeutic Products Act (PMD Act). This Act provides the option of a new pathway to obtain conditional and time-limited approval for "regenerative medical products," which takes into account the high degree of quality variability of cells in the products and therapies that fall under this classification (Figure 1) (Hara et al., 2014). The approval review process will adopt a 9-month target for regulatory review time (http://www.pmda.go.jp/files/000155330.pdf), following expansion of the PMDA (from 751 people to 1,065 people) (http://www.mhlw.go.jp/kouseiroudoushou/shokanhoujin/dokuritsu/shiryou02/dl/kyouka01.pdf). As a result, the review period for products under the PMD Act will be shorter than that of already approved products in Japan. However, to obtain conditional and time-limited approval, exploratory clinical trials are required to predict reasonable likelihood of clinical benefit (for example, by using a surrogate endpoint); this is consistent with the US Food and Drug Administration's (FDA's) accelerated approval scheme for serious or life-threatening illnesses (http://www.fda.gov/ForPatients/Approvals/Fast/ucm405447.htm). The European Agency is putting forward the concept of adaptive licensing as a flexible approach to product approval, which is prospectively planned, and where uncertainty is reduced through the collection of post-approval data on the medicine's use in patients (Eichler et al., 2012; http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000601.jsp). In The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) member regions, regulatory agencies have tried to respond to patient/medical needs by developing an early access scheme to new therapies, weighing the safety and efficacy of the products in relation to the product life cycle (Table S1). From this perspective, conditional and time-limited approval is quite in line with global regulatory trends to resolve unmet medical needs. Overseas enterprises may also participate in the new Japanese regulatory system.

A confirmatory clinical study and followup patient safety measures, including restrictions on clinical institutions that may use the treatment, must follow the conditional and time-limited approval, in preparation for a further approval process within a maximum period of 7 years. In order to ensure that products with unconfirmed effectiveness do not remain on the market, the new regulation gives MHLW/PMDA a clear legal authority to withdraw approval during the second approval process. The scope of regenerative medical products is considered to be mainly products satisfying unmet medical needs (including orphan indications and serious or life-threatening illnesses), which may also require a surgical procedure in some cases. Because of these circumstances, conventional drug regulation may not necessarily be applicable and a more flexible approach to safety and efficacy evaluation is called for. The sponsor is also encouraged to engage in regulatory consultation, since the design of further clinical studies and how best to demonstrate effectiveness may depend on the individual product, in terms of the indicated use, population, and mode of action and medical environment. At the

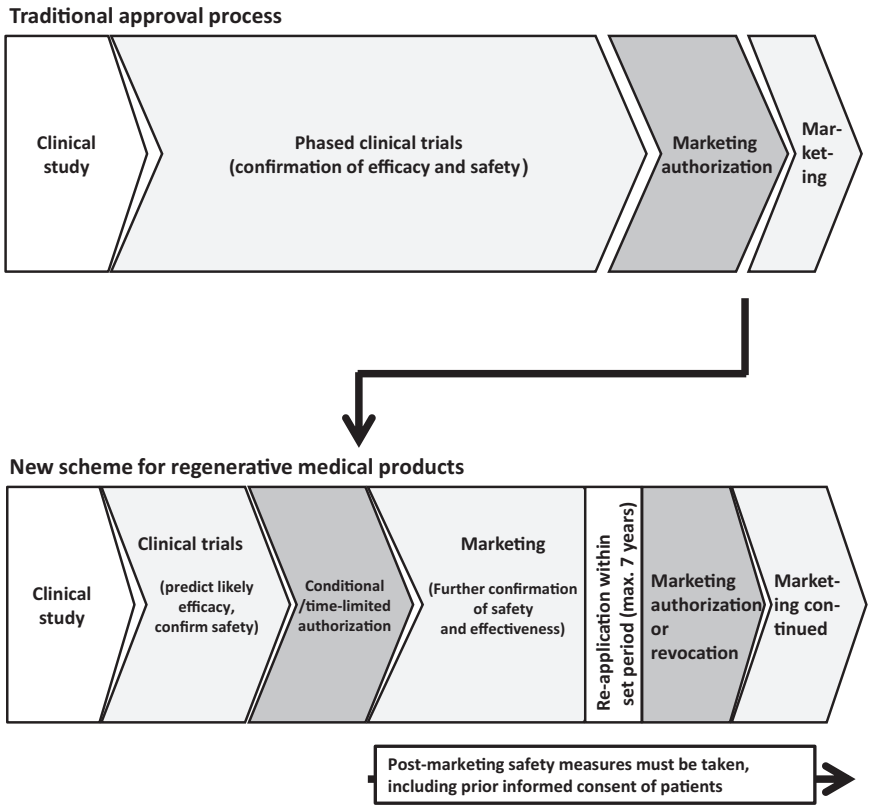

Figure 1. New Approval Process for Regenerative Medical Products
Under the traditional approval process, long-term data collection and evaluation in clinical trials for regenerative medical products are needed, and so a new, separate approval process has been created. If an exploratory clinical trial predicts likely clinical benefit, the regenerative medical product will be given conditional, time-limited approval.

same time, the MHLW and PMDA will establish a public patient registry system to support more accurate studies on post-marketing safety and efficacy in patients treated with regenerative medical products (http://www.mhlw.go.jp/stf/shingi/0000050197.html).

Regenerative medical products that are approved under the PMD Act will not be subject to the Act on the Safety of Regenerative Medicine (except for off-label use) insofar as they are being used within the conditions of their approval. The concrete reimbursement policy for the products granted conditional and time-limited approval is being worked out at the Central Social Insurance Medical Council, following the Council's discussion in November 2014 to open the door to reimbursement and pricing for these products.

These two laws represent an attempt by Japan to promptly deliver regenerative medicine to patients while ensuring the efficacy and safety of application of regenerative medicine.

SUPPLEMENTAL INFORMATION

Supplemental Information for this article includes one figure and one table and can be found with this article online at http://dx.doi.org/10.1016/j.stem.2015.03.012.

WEB RESOURCES

The URLs for data presented herein are as follows:

European Medicines Agency. "Adaptive pathways." http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000601.jsp

Food and Drug Administration. "Accererated approval." http://www.fda.gov/ForPatients/Approvals/Fast/ucm405447.htm

MHLW. "The Act on the Safety of Regenerative Medicine." http://www.hourei.mhlw.go.jp/cgi-bin/t_docframe2.cgi?MODE=hourei&DMODE=SEARCH&SMODE=NORMAL&KEYWORD=%8d%c4%90%b6%88%e3%97%c3%93%99&EFSNO=229&FILE=FIRST&POS=0&HITSU=306

MHLW. "Pharmaceuticals, Medical Devices and Other Therapeutic Products Act." http://www.hourei.mhlw.go.jp/cgi-bin/t_docframe.cgi?MODE=hourei&DMODE=CONTENTS&SMODE=NORMAL&KEYWORD=&EFSNO=638

MHLW. "Press release of PMDA's human resources expansion by 2018." http://www.mhlw.go.jp/kouseiroudoushou/shokanhoujin/dokuritsu/shiryou02/dl/kyouka01.pdf

MHLW. "Report on Patient Registry System of regenerative medical products, 2014" http://www.mhlw.go.jp/stf/shingi/0000050197.html

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